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09/892,613	06/27/2001	Shawn Shui-on Leung	655	4914

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EXAMINER

HELMS, LARRY RONALD

ART UNIT

PAPER NUMBER

1642

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/892,613	LEUNG, SHAWN SHUI-ON
	Examiner Larry R. Helms	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 21 October 2002.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) 14, 15 and 20-24 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-13 and 16-19 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1,5,11.

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.  
 5) Notice of Informal Patent Application (PTO-152)  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

***Election/Restrictions***

1. Applicant's election with traverse of Group I, claims 1-13 and 16-19, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the examiner states that inventions of groups I and I-III are distinct. This is not persuasive because this was not stated in the restriction. The restriction stated I and II-III are product and process of making and as stated the antibody of group I can be made by a materially different method. The response states that no factual evidence is provided for the distinction of inventions I and IV-V. this is not persuasive because as stated the antibody can be used in a materially different method. The response then concludes as stating the examiner has not demonstrated a serious burden. This is not persuasive. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 14-15, 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

3. Claims 1-13 and 16-19 are under examination.

***Specification***

4. The abstract of the disclosure is objected to because Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

Correction is required. See MPEP § 608.01(b).

***Claim Objections***

5. Claims 2, 4, 5 and 6-13 are objected to because of the following informalities:

- Claims 4 and 5 contain the term "claim (1)" and it should be "Claim 1".
- Claims 6-13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should be in the alternative. See MPEP § 608.01(n). Accordingly, the claims have been interpreted as being in the alternative for examination on the merits.
- Claims 2, 4, and 6 need to end with a period.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 and those dependent from claim 1 are indefinite for reciting "immunoglobulin containing the heavy and/or light chain" in line 2 of claim 1 and "heavy and light chain" in line 6 of claim 1. Does the claim require both or not and if not does the phrase in line 6 mean one can replace a heavy chain FR with a light chain FR?

b. Claim 1 and those dependent on claim 1 are indefinite for reciting "affinity comparable to" in claim 1 because the exact meaning of the phrase is not clear. Does the phrase mean the same affinity or within 10 fold or some other value and in addition, are the re-engineered and parent antibody affinity determined by the same method?

c. Claim 1 recites the limitation "said re-engineered immunoglobulin chain" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

d. Claim 1 recites the limitation "said different immunoglobulin chain" in claim 1.

*T* There is insufficient antecedent basis for this limitation in the claim.

e. Claims 2-5 are indefinite for reciting "positions known to be close to" in the claims because the exact meaning of the phrase is not clear. Does the phrase mean close in the linear amino acid sequence or in the tertiary sequence and what defines the distance to be "close"?

f. Claims 4 and 5 are indefinite for reciting "conservatively similar amino acids...at the three amino acids immediately adjacent to the flanking CDRs" in claim 4 because the exact meaning of the phrase is not clear. It is unclear if the list of amino acids in claim 4 are the conservative amino acids and if so gly is not a conservative amino acid with tyr. Does the phrase mean the three amino acid positions are conservative among themselves or are the three amino acids conservative between the FR chosen and the parent FR?

g. Regarding claim 4, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

h. Claims 4 and 5 are indefinite for reciting "preferably 100%" because it is not clear if the sequence homology is to be 100%.

i. Claims 6-9 and those that depend from these claims are indefinite for reciting "wherein the back mutated amino acids" in the claims because the exact meaning of the phrase is not clear. What are "back mutated amino acids" and where are they from, the donor or acceptor or some other source?

8. Claims 16-19 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does

not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of hpRFB4 and hp1F5 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different  $V_H$  chains (about 50% homologous) can combine with the same  $V_K$  chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different  $V_H$  sequences combine with different  $V_K$  sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species hpRFB4 and hp1F5. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

- (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;
  
- (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

9. Claims 1-13 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a re-engineered or FR-patched immunoglobulin that contains all 6 CDRs from a parent antibody in the correct order and spaced between framework regions from an acceptor immunoglobulin and compositions comprising such and a re-engineered antibody of hpRFB4 and hp1F5 with successful completion of the biological deposit requirements and compositions comprising such, does not reasonably provide enablement for a re-engineered or FR-patched immunoglobulin that does not contain all 6 CDRs from the light chain and the heavy chain of a parent antibody spaced between frameworks of a acceptor immunoglobulin and pharmaceutical compositions comprising such or pharmaceutical compositions comprising hpRFB4 and hp1F5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a re-engineered immunoglobulin that contains either a heavy chain or a light chain variable region sequence from a parent antibody

and pharmaceutical compositions comprising such. Claim 1 broadly encompasses replacing a heavy or a light chain FR with a light chain or heavy chain FR respectively. The specification teaches an immunoglobulin that was humanized and the immunoglobulin contains both the heavy and light chain CDRs from a parent immunoglobulin (see Example 1). The specification does not enable an immunoglobulin as broadly claimed.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that

immunoglobulins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claims 13 and 19 encompass pharmaceutical compositions comprising an immunoglobulin. The claims are drawn to a pharmaceutical composition comprising an immunoglobulin. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions is for therapeutic treatment of diseases including cancer. Thus, the nature of the invention is a therapeutic composition used in the treatment of disease, such as cancer.

Although the specification discloses the claimed composition, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of diseases such as cancer. The specification does not teach a correlation of in vitro to in vivo data. Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Immunother., 1994, see Introduction). Results obtained under controlled conditions and

in inbred animals often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. The specification does not disclose whether the treatment is effective in animals with pre-existing cancer, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of pre-existing neoplasia, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph).

Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition/vaccine effective for its intended use.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

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10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Queen et al (U.S. Patent 5,693,762, issued 12/97, IDS #1 ½).

The claims are summarized as a re-engineered antibody comprising a heavy and light chain from a parent antibody and Fr from a different species wherein the Fr are from two different sources and the re-engineered immunoglobulin binds antigen with affinity within 3 fold of the parent, further claimed is the FR chosen exhibits the highest homology to the parent FR and the three or four amino acids immediately adjacent to the CDRs are identical and contains identical amino acids at positions known to be close to or interact with the CDRs from a crystal structure, or contain conservatively similar amino acids at the three or four amino acids immediately adjacent to the CDRs, or contains framework residues re-introduced into the antibody which are from the donor wherein the re-introduced amino acids are within 4Å, 5Å, or 6Å of a CDR or is typical at that position for the donor, wherein the affinity is  $10^8 M^{-1}$  to  $10^{10} M^{-1}$ , wherein the immunoglobulin is pure, and compositions comprising such.

For this rejection the intended use for a pharmaceutical composition is given no patentable weight. For this rejection the term “adjacent” is interpreted to be amino acid residues next to a CDR in linear amino acid sequence.

Queen et al teach humanized antibodies wherein the framework regions are from humans and the donor are from another species. Queen et al teach several criteria for humanization and those are that the acceptor FR is highly homologous, 60-70% to the donor (see column 2, lines 45-55), the human FR residue will be one or more residues that are immediately adjacent to the CDRs, or at 4-6 Å from the CDR (see column 3, 14, lines 25-60), or at a position that is rare for the donor relative to the human sequence (see column 3, lines 20-26), and the affinity is  $10^8 \text{ M}^{-1}$  or higher and may be within 2 fold of the parent antibody (see column 3, lines 35-42), and the FR can have conservative substitutions (see column 12, lines 20-26), and the antibody comprises amino acids re-introduced from the donor (see column 12, lines 39-44), and the antibodies are substantially pure and compositions comprising such. Queen et al also teach the importance of residues immediately adjacent to a CDR or those residues that interact with a CDR which are important for affinity and computer programs to create such models of antibodies (see column 15, lines 60).

### ***Conclusion***

12. No claim is allowed.
  
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00

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am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

A handwritten signature in black ink, appearing to read "Larry R. Helms".